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Disrupting the Stem Cell Niche: Good Seeds in Bad Soil

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Stem cells reside in a microenvironment or niche that is critical for stem cell maintenance and regulation. But what happens when a stem cell niche is disrupted? In this issue of *Cell*, two reports (Walkley et al., 2007a, 2007b) demonstrate in mice that alterations in the niche for hematopoietic stem cells lead to the development of myeloproliferative disease.

Hematopoietic stem cells (HSCs) are maintained and regulated in microenvironments or niches in the bone marrow. HSCs are known to reside in two different niches, an "osteoblastic" niche and a "vascular" niche. In the osteoblastic niche, HSCs are associated with a subset of osteoblasts (the cells responsible for bone formation) that line the inner surface of the bone cavity (Calvi et al., 2003; Zhang et al., 2003; Arai et al., 2004). In contrast, in the vascular niche, HSCs associate with the surfaces of endothelial cells that line the sinusoids of bone marrow and spleen (Kiel et al., 2005). Recently, it was shown that CXCL12-abundant reticular (CAR) cells are found in association with HSCs in both the osteoblastic and vascular niches (Sugiyama et al., 2006) and may serve as a transit pathway for shuttling HSCs between the two. It has been proposed that these two niches are functionally distinct: the osteoblastic niche is thought to maintain HSC quiescence over the long term, whereas the vascular niche is thought to maintain HSCs over a shorter time period, supporting HSC proliferation, favoring myeloid and megakaryocytic lineage differentiation, and mediating HSC circulation (Kopp et al., 2005). Despite the critical role of these two niches in regulating HSCs, evidence for a role of the niche in disease has been limited. In this issue of *Cell*, Orkin, Purton, and their colleagues demonstrate in mice that the microenvironment can play a dominant role in the development of myeloproliferative disease—a disorder characterized by the neoplastic development of myeloid cells (Walkley et al., 2007a, 2007b) (Figure 1).

Given that key cell cycle regulators have been implicated in HSC dysfunction, Orkin and colleagues first examined loss of the retinoblastoma (RB) protein, a cell cycle regulator and tumor suppressor, in the hematopoietic system (Walkley et al., 2007a). Surprisingly, RB was found to be dispensable for self-renewal and multilineage differentiation of HSCs. However, widespread loss of RB in the hematopoietic system results in extramedullary hematopoiesis (hematopoiesis outside of the bone marrow, for instance, in the spleen). These mice eventually develop myeloproliferative disease. Strikingly, myeloid-specific loss of RB resulted in only mild defects and did not result in myeloproliferative disease or HSC abnormalities, suggesting that the defect resulting from widespread loss of RB is not solely caused by myeloid cells with intrinsic RB deficiency or by myeloid cells derived from RB-deficient HSCs. Furthermore, transplantation of normal hematopoietic cells into an RB-deficient microenvironment failed to recapitulate the effects observed with widespread deletion of RB. Only when myeloid-specific loss of RB was combined with loss of RB in the microenvironment was the full myeloproliferative defect recapitulated. Thus, the myeloproliferative disease observed with widespread loss of RB resulted from an interaction between myeloid cells and the altered microenvironment.

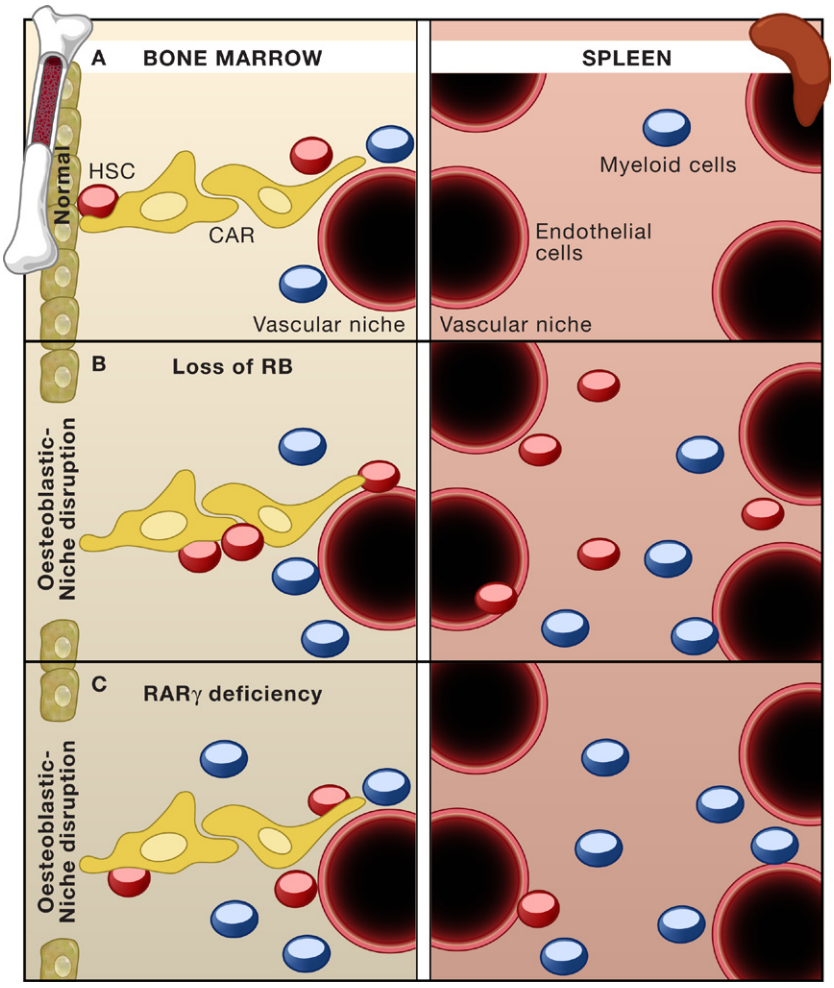

Figure 1. Alterations to the Stem Cell Niche Lead to Myeloproliferative Disease
(Top) In normal bone marrow, the osteoblastic niche (tan) maintains hematopoietic stem cells (HSCs) (red) in a quiescent state. Endothelial cells line the bone marrow and spleen sinusoids CXCL12-abundant reticular (CAR) cells (yellow) are found in association with HSCs in both the osteoblastic and vascular niches (Sugiyama et al., 2006) and may serve as a transit pathway for shuttling HSCs between the osteoblastic and vascular niches where essential but different maintenance signals are provided. (Middle) Loss of RB expression in the microenvironment and myeloid cells leads to degradation of the osteoblastic niche by osteoclasts (Walkley et al., 2007a). HSCs are now displaced from their homeostatic niche and undergo expansion and mobilization to the spleen, where myeloid development predominates, eventually resulting in myeloproliferative disease. Eventually, HSCs are exhausted, resulting in bone marrow failure. (Bottom) RARγ deficiency also results in depletion of the osteoblastic niche (Walkley et al., 2007b). Here, myeloid progenitors (blue) predominate and undergo massive expansion in the spleen. HSCs are maintained in the vascular niche, but excessive myelopoiesis in bone marrow and spleen leads to myeloproliferative disease.

Osteoclasts, which are the cells involved in bone resorption, belong to the myeloid cell family. The number of osteoclasts increased dramatically following the loss of RB, which resulted in depletion of osteoblasts. Indeed, histopathology of bone sections showed that RB deficiency resulted in a loss of trabecular bone, the primary site of the osteoblastic niche. Thus, it appears that RB loss ultimately results in loss of the niche, which is thought to maintain HSC quiescence, leading to HSC mobilization and extramedullary hematopoiesis, possibly setting the stage for myeloproliferative disease.

In a complementary study, Purton and colleagues examined the effects of retinoic acid receptor γ (RARγ) deficiency on the hematopoietic system of mice (Walkley et al., 2007b). RARγ deficiency also resulted in myeloproliferative disease. In this case, the disease was due entirely to deficiency of RARγ in the microenvironment. As with the loss of RB, RARγ deficiency also led to a reduction in trabecular bone. Could loss or reduction of the osteoblastic niche link these two models of myeloproliferative disease? Although this is an important connection between the two models, the story is more complicated. Older mice lacking RARγ exhibit nearly complete loss of trabecular bone and also exhibit mobilization of HSCs to the spleen, but the defect is reported to stem primarily from relatively mature myeloid progenitor cells. Nonetheless, subtle defects in more primitive hematopoietic stem and progenitor cells may be the root cause of disease in this model. However, unlike the RB model system, which exhibits hematopoietic failure, HSCs are retained in the bone marrow of RARγ-deficient mice and continue to support hematopoiesis for months. It is unclear why the vascular niche fails to maintain HSCs in the RB model and in other models in which osteoblasts are severely reduced. However, it is likely that loss of RB or RARγ has broad effects on the microenvironment that are not limited to a reduction in the osteoblastic niche. Indeed, Purton and colleagues demonstrate this by showing that the effect of RARγ deficiency in the microenvironment is reduced in mice that receive transplants of TNFα null HSCs as compared to wild-type HSCs, although the reason for this is not clear. Even though HSCs are maintained for months despite a severe reduction in the osteoblastic niche, the consequences of this changed microenvironmental regulation of HSCs in the RARγ-deficient mice likely sets the stage for development of myeloproliferative disease.

Myeloproliferative disease, although not malignant, is a preleukemic condition. Thus, these findings raise the question of whether changes in the HSC niche have a role in hematopoietic malignancy. Although neither model reported here results in leukemic transformation, evidence that the microenvironment contributes to tumorigenesis is accumulating. It has been proposed that many cancers are derived from and supported by cancer stem cells. Cancer stem cells are derived from normal

stem cells and have uncontrolled self-renewal capability that is independent of the niche. Alternatively, progenitors may inappropriately retain or acquire self-renewal capacity and become cancer stem cells. A complementary concept of a tumorigenic niche has been proposed (Flynn and Kaufman, 2007; Li and Neaves, 2006). Niche dysfunction could contribute to tumorigenesis in several ways. For instance, a tumorigenic niche could supply inappropriate levels of growth factors that either promote proliferation and/or inhibit apoptosis. Indeed, bone marrow is a preferred site for metastasis of certain cancers (Jones et al., 2006). In addition, an important difference between normal and neoplastic HSCs is their degree of dependence on the niche. The osteoblastic niche is thought to maintain HSC quiescence by providing signals that inhibit proliferation. Thus, loss of this niche as reported in the RB- and RARγ-deficient mice may lead to stem cell (or its derived progenitor cell) expansion due to the loss of inhibitory signals normally provided by the osteoblastic niche. Mobilization of stem and progenitor cells, mainly to the spleen, may provide a more permissive microenvironment favoring cellular proliferation and myeloid differentiation that aids in the development of myeloproliferative disease. The fact that leukemia fails to develop in these mouse models suggests that additional genetic mutations may be necessary for complete transformation. It will be important to determine the contributions of the microenvironment to other hematological disorders, as they are likely to be significant and may provide new targets for therapy. Finally, the efficacy of bone marrow transplantation, commonly used to treat many hematological disorders, may be decreased in cases where substantial microenvironmental dysfunction contributes to disease. Thus, further knowledge of contributions of the stem cell microenvironment to disease will be important for future clinical progress.

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A Specialized Nucleosome Has a "Point" to Make

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Three recent papers, including Mizuguchi et al. (2007) in this issue, show that the nonhistone protein Scm3 is required for the recruitment of the histone H3 variant Cse4 to centromeres in budding yeast. Scm3 forms a chromatin component with Cse4:histone H4 tetramers that appear to lack H2A/H2B histones. These studies provide key insights into the pathway that recruits Cse4 to centromeres and have important implications for other functions of chromatin.

Centromeres are special chromosome loci where kinetochores are assembled during mitosis and meiosis. All eukaryotes contain a centromere-specific histone H3 variant (CENP-A) that replaces canonical histone H3 at centromeric nucleosomes, forming a structural foundation for the kinetochore. CENP-A:H4 tetramers are structurally differ-